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DECOMPRESSION SICKNESS AND BUBBLE FORMATION IN BLOOD AND TISSUES*

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E. NEWTON HARVEY

Henry Fairfield Osborn Professor of Biology,
Princeton University

INTRODUCTION

After the last World War, 1914–1918, an editorial in the *Journal of the American Medical Association*, in referring to medical aspects of aviation and praising the work that had been done to protect aviators against the effects of altitude, spoke of the necessity of speed and the ability to climb above an opponent. At that time bombing and observation planes flew "for hours at altitudes of 12,000 to 15,000 feet" while pursuit planes attained "the enormous altitude of 18,000 and 20,000 feet".[1] In the second World War a service ceiling of well over 40,000 feet has been attained, a height where even the breathing of pure oxygen is not sufficient to supply the needs of the body. Without the protection of a pressurized cabin, man has become the limiting factor to high ascent.

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Princeton University.

But considerably below 40,000 feet, a series of symptoms have been described which cannot be attributed to any one of the three common and obvious difficulties at great height: (1) lack of oxygen; (2) ear and sinus trouble, due to non-equalization of pressure between middle ear (or sinuses) and the external atmosphere; (3) intestinal pains, due to the expansion of gas in the digestive tract. A fourth group of additional symptoms may appear and affect various parts of the body. These range from a mild rash or ache to unbearable pain near the joints, from tightness in the chest to serious coughing spells and from hyperesthesias or anesthesias to convulsions, paralysis and syncope. The individual is definitely incapacitated, sometimes seriously. Since the symptoms may begin to appear as low as 25,000 feet and are marked at 35,000 feet, they limit the altitude at which an open plane can be flown, for these heights are well below the point (38,000 ft.) at which pure oxygen just begins to fail in supplying the retina and brain. Any of the above group of symptoms, fully described in Armstrong's[2] classic book on Aviation Medicine, constitute decompression sickness* since they result from decompressing the body from one atmosphere to lower values, an analogous change to the return of a person to one atmosphere after a previous exposure to compressed air. Decompression sickness may also be applied to the symptoms resulting from the latter change, although the older terms, compressed air illness or caisson or diver's disease, have been more frequently used.

In both compression-decompression experiments and in low pressure or "altitude" experiments, excess gas is dissolved in the body. The tissues are saturated at a certain gas pressure, producing a similar tension of dissolved gas in the cells and tissues, and then the gas pressure is decreased. The procedure can be compared to removing the cap from a soda water bottle or exhausting a tube of water with an air pump. Under certain conditions bubbles will form in both cases. It has long been recognized and appears quite certain that compressed air illness is due to bubble formation in blood and tissues. By analogy the symptoms at high altitude might also be expected to result from bubbles, although the question, until recently, had by no means been settled and other theories had been proposed. Indeed, the formation of bubbles in animals at low barometric pressures had been

* Armstrong[2] has suggested the word aeroembolism, but this term implies unproven ideas about the origin of the symptoms.

denied by the father of barometric studies, Paul Bert.

Early in the organization of the Committee on Medical Research, the division of Aviation Medicine foresaw the seriousness of decompression symptoms and established the Subcommittee on Decompression Sickness, with John F. Fulton, of Yale University, as able Chairman. The present basic study was undertaken in order to separate and analyze the fundamental factors involved in the formation of bubbles, with special reference to the conditions found in animals, and with the purpose of applying the findings to the aviator. Critical terminal experiments can be carried out with animals that cannot be undertaken with man. Moreover, the whole problem of bubble formation in liquids was in a little known state at the time this work was started in May, 1942.

Many other groups of investigators have been sponsored by this Subcommittee. It is not possible, for security reasons, to refer to the vast amount of detailed data collected by these groups. The reader is referred to reports that will eventually be published, prepared under the direction of the responsible investigators–Behnke, Bronk, Blankenhorn and Ferris, Evans, Fulton, Greeley, Harvey, Hitchcock, Ivy, Jacobs, Knisley, Lawrence and Hamilton, Scott, Swindle, Whitaker, Blinks and Twitty–as well as the many Army and Navy experimental and training stations in this country, in Canada and in England.

It is a pleasure to express here my sincere appreciation of the keen interest, fertile ideas and extended experimentation of the men who have collaborated on the Princeton project.* Wm. D. McElroy and Mr. A. H. Whiteley, members for the full period of the contract, and D. C. Pease, G. H. Warren, K. W. Cooper and Wm. Kleinberg, part of whose time has been devoted to the work. I am also particularly grateful to Professor Henry Eyring, of the Chemistry Department, Princeton University, for much helpful discussion, and especially to Mr. D. K. Barnes, who has worked out a detailed theory of the separation of a gas phase from a liquid and clarified our knowledge of the conditions for stability and growth of gas masses.

History

Probably the first bubble recorded in animals was that seen by

* The results of this work have been published in a series of papers in the *Journal of Cellular and Comparative Physiology*, Aug.-Dec., 1944.

Robert Boyle[3] in the eye of a snake which he had placed under his newly invented air pump in 1670. Boyle's remarks are so pertinent to our subject and so prophetic of what has now been realized in aviation that I quote him in full. After describing an experiment with fresh blood and another with fresh milk which boiled vigorously on evacuation with his pneumatical engine, he says:

> *Note,* that the two foregoing Experiments were made with an Eye cast upon the inquiry, that I thought might be made; Whether, and how far the destructive operation of our Engin upon the included Animal, might be imputed to this, that upon the withdrawing of the Air, besides the removal of what the Airs presence contributes to life, little Bubbles generated upon the absence of the Air in the Blood, juices, and soft parts of the Body, may by their Vast number, and their conspiring distension, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones, that convey the Blood and Nourishment; and so by choaking up some passages, and vitiating the figure of others, disturb or hinder the due circulation of the Blood? Not to mention the pains that such distensions may cause in some Nerves, and membranous parts, which by irritating some of them into convulsions may hasten the death of Animals, and destroy them sooner by occasion of that irritation, than they would be destroyed by the bare absence or loss of what the Air is necessary to supply them with. And to shew, how this production of Bubbles reaches even to very minute parts of the Body, I shall add on this occasion (hoping that I have not prevented my self on any other) what may seem somewhat strange, what I once observed in a *Viper,* furiously tortured in our Exhausted Receiver, namely, that it had manifestly a conspicuous Bubble moving to and fro in the waterish humour of one of its Eyes.

Although sporadic observations were made after Boyle, real knowledge of the effects of varying atmospheric pressures began with Paul Bert's systematic study, published as *La pression barométrique* in 1878.[4] Bert demonstrated the presence of bubbles in the blood and tissues of animals after compressed air experiments but denied the existence of such bubbles in animals exposed to low pressures, although Hoppe[5] in 1857 had previously reported bubbles to be present in animals at 50 mm. Hg. (62,000 ft.). To further study the problem, Hill and Greenwood[6] in 1910 exposed eight mice, two guinea pigs, a kitten and a rabbit to 50 mm. Hg air pressure until the animals died and then examined them post-mortem. No bubbles were found in any except the rabbit whose heart and large vessels were full of air. They concluded that in general Paul Bert was right. Actually, both Hoppe and Bert were correct for we now know that resting animals at high altitudes rarely develop bubbles but if they are exercised with vigorous muscle contraction, bubbles appear in the blood quite regularly. These conflicting results, as well as the doubts expressed by various workers that bubbles appear in blood at altitudes, must be attributed to the chance variation in amount of movement tak-

ing place in the animals under experimentation.

The bad effects of deep diving have long been known but the problem of illness after exposure to high air pressures became particularly important with the invention in 1840 of the caisson, a compressed air chamber for sinking shafts or tunnels or for building piers under water. With the extended use of this device and the compressed air diving suit in the latter part of the last century, diver's or caisson disease became common. A series of words were coined by the workers to describe the symptoms. Among these the "bends," the "chokes" (or "chokers"), the "itch" and the "staggers" are the most picturesque and describe quite adequately joint pains, respiratory difficulties, skin eruptions and paralyses. The experience from actual flying and in high altitude chambers indicates that all the above symptoms may also occur. Skin trouble and nervous affections are rather rare but the bends and chokes are frequent and these words have become a permanent part of the scientific vocabulary of the subject.

Interest of the British Admiralty in diving led J. S. Haldane[7] with Boycott and Damant[8,9] as well as Leonard Hill[10] to their extensive research in 1906 to 1908 while in the United States, beginning in 1935, Behnke[11,12] and associates, Shaw, Willmon and Yarborough and Shilling,[12a] have extended our knowledge, making special studies of nitrogen elimination, fat content and the use of helium for unusually deep diving to eliminate the dangers of oxygen poisoning and nitrogen narcosis. In Germany the classic contribution of Heller, Mager and von Schrotter[13] compiles the facts on diving up to 1900.

The symptoms of caisson disease could be immediately alleviated and a life often saved by recompressing the patient and then decompressing more slowly, allowing time for excess gas to be removed from the body. Chambers for this purpose were first introduced by Sir Ernest Moir about 1890. The increased pressure contracts the bubbles and this fact proves that symptoms only appear when bubbles reach a certain size. Experience at simulated high altitudes likewise indicates that recompression to lower altitudes (even a change from 35,000 to 25,000 feet) will also instantly relieve bends and chokes but upon immediate reascent the pain will reappear in exactly the same place.

Such facts lead to the inescapable conclusion that decompression sickness results from the formation of gas bubbles in the body and

multiplicity of symptoms reflects the region in which the bubbles grow or lodge. The relief or treatment of decompression sickness is an accomplished procedure–immediate recompression. Prophylaxis remains to be considered. If bubble formation could be prevented in the body when its tissues are supersaturated, bends would cease to be a problem.

It is obvious that a fundamental study of the conditions under which gas will separate from solution is absolutely essential. In addition the composition of the gas which forms the bubbles must be known and every possible fact that might bear on the problem. Consequently, a study of bubble formation has been undertaken under the simplest conditions easily attainable, in water saturated with a single gas in a glass vessel. This study has been supplemented by investigations of blood *in vitro* and also in the body of narcotized animals, for it is in this fluid, i.e., in the blood vessels, that bubbles most frequently occur. The condition may be called pompholyhemia and we have used this symptom in our study of the cat as an index to evaluate similar procedures which might cause or prevent decompression sickness in man.

Bubble Formation From Excess Gas

Many important principles can be demonstrated with a bottle of soda water in which carbon dioxide is dissolved at a tension of 3 or 4 atmospheres. If the chilled bottle has remained upright and undisturbed for some time, no bubble will form when the cap is removed but on tipping the bottle so that soda water flows over the dry glass surface bubbles immediately appear, and on carefully pouring into a dry tumbler abundant bubbles cling to the walls. There may frequently be observed a chain of bubbles arising from a point where a gas mass remains sticking to the glass. Sometimes bubbles also arise from a clearly visible dust particle in the bulk of the liquid. If the tumbler is greasy, the hydrophobic region will be outlined by abundant bubbles which persist until the soda water has lost its excess gas. In fact this "bubble test" will tell how thoroughly a tumbler has been washed.

The bubbling and effervescence is all due to minute gas masses which stick to the dry walls or to dust particles and grow into bubbles as soon as the pressure release occurs. We can prove this

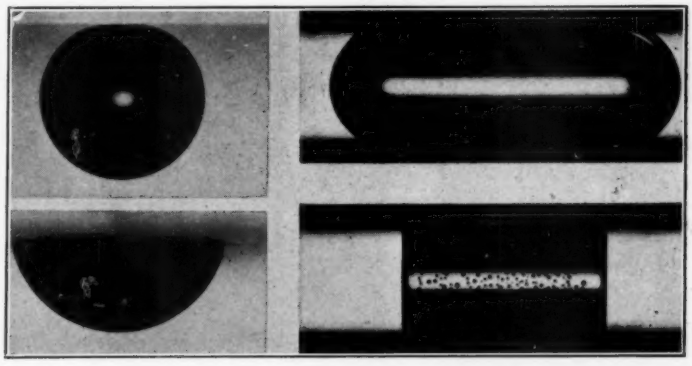

Fig. 1 Fig. 2

Fig. 1 (left). Photograph of an air bubble under a glass (above) and a paraffin surface (below).

Fig. 2 (right). Photograph of an air bubble in a glass capillary (above and a hydrophobic capillary (below). In the latter the concave curvature of the air surface cannot be seen but it is indicated by the fact that the transmitted white band of light does not reach the edge of the gas cylinder. The air bubble on glass is 1.65 mm. across.

by gently pouring the soda water into a scrupulously *clean* and *wet* tumbler, when no bubbles form, except during the first disturbance of the surface due to pouring. If some dry powder, such as infusorial earth, is now dropped into the quiet soda water the carbon dioxide separates with explosive violence but if the infusorial earth has been first boiled in water to remove its air films and then placed while wet into the soda water, not a single bubble will appear. However, a paraffined surface (hydrophobic), no matter how well cleaned, will always bubble profusely.

Gas Nuclei

These effects are all due to small gas masses, or gas nuclei, which stick to any dirty, especially greasy, surface but not to clean wet glass. The sticking of gas is a matter of contact angles, which are well seen from the form of bubbles in capillary tubes or on surfaces. As shown in Figure 2, a bubble in a glass capillary filled with water has rounded (convex) ends—the contact angle (measured through the water) is zero; in a paraffined capillary the gas bubble has concave ends and

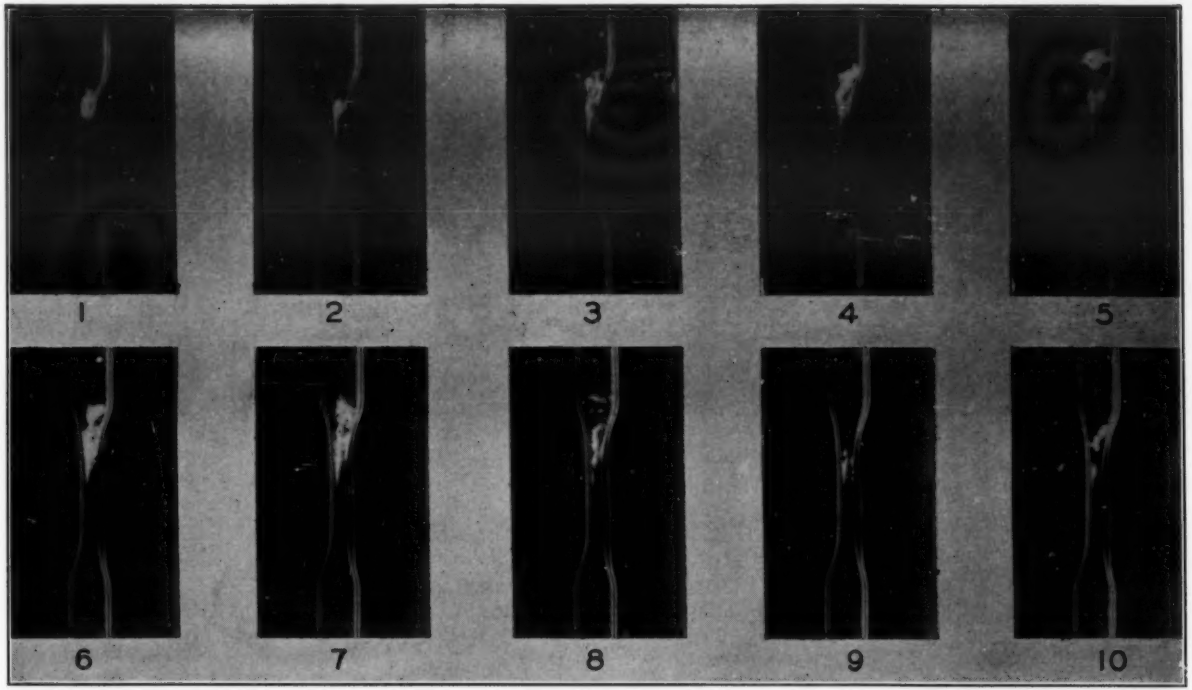

Fig. 3. Negative prints from a high-speed movie (1,680 frames per second) of cavitation in a Reynolds' tube of 10 mm. large diameter. Flow from bottom to top. Note the periodic cavitation (white in appearance) beginning at a particular spot on the narrow region of the tube. The individual frames are numbered.

the contact angle is about 108°. Since the form of gas bubbles in blood vessels is similar to that of water in a glass tube, we may conclude that the endothelium is, on the average, hydrophilic, an important fact for the theory of bubble formation.

On a plane surface the form of bubbles is illustrated in Figure 1 and the contact angles are clearly visible. On a completely hydrophobic surface like glass, the zero contact angle means that no bubble can stick and no nucleus can remain but with any positive contact angle nuclei can stick and may be stable under certain conditions.

Bubble Formation From Negative Pressure

The development of bubbles in a liquid saturated with gas at one atmosphere and under one atmosphere pressure is uncommon but a number of examples are known. Such bubble formation is due to local decrease in hydrostatic pressure. A most interesting case was described by Osborne Reynolds[14] at a constriction in a pipe. When water flows through a tube which is narrowed at one place, the velocity is obviously increased at the constriction and, by Bernoulli's law, the pressure must decrease. In addition, violent turbulence and vortices appear.* If the constriction is narrow enough and the velocity sufficient, very low pressures will be produced and the water will suddenly break into cavities (cavitation) with a hissing sound. When the cavities collapse, which they do periodically, as shown in Figure 3, bubbles of gas remain and can be seen in the water leaving the constriction. Reynolds called the phenomenon "the boiling of water in an open tube at ordinary temperature." Whenever a local constriction occurs in a blood vessel, whether from a spasm or from passive squeezing between muscles, the pressure must be lowered at the constricted point, but it is doubtful if the velocity of flow is sufficient to produce Reynolds' cavitation in the body.

Another example is the cavitation which appears in water due to the passage of intense sound waves, or the bubbles which will form in a test tube of water at one atmosphere pressure if the bottom is hit a series of blows. Just as sound waves are made up of pressure changes, with increased followed by decreased components, so the series of blows involve increased followed by decreased pressure. A blow (or even vibration) to the human body at altitude would

* Dean[14a] believes most bubble formation in water free of gas nuclei is due to vortices.

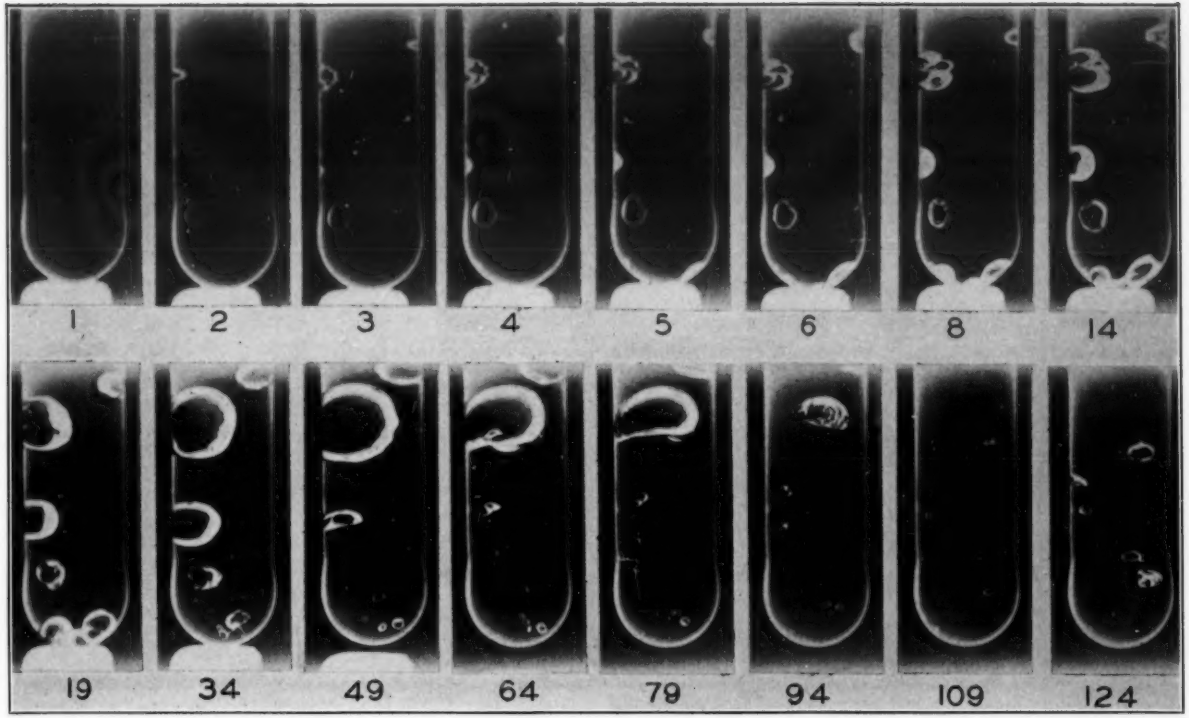

Fig. 4. Negative prints from a high-speed movie (1,200 frames per second) film of cavity formation in a glass tube (19.3 mm. diam.) filled with air saturated water but under a low pressure, when the bottom is struck a blow. The initial cavity oscillates in volume several times before the final bubbles start rising to the surface. The individual frames are numbered.

tend to bubble formation, but might not necessarily actually produce bubbles unless intense.

Whenever tensions are built up, as when a glass rod immersed in water is suddenly withdrawn, or when a propeller blade by rotation continually pulls away from the water, cavities may be formed and bubbles appear.

If the liquid, already supersaturated with gas, is subjected to a blow or any other treatment described above, the formation of bubbles is greatly facilitated. The results of cavitation become particularly important at high altitudes where the pressure is already near the vapor pressure of water, much less in compression-decompression experiments where the final pressure is one atmosphere, far from the vapor pressure of water. A series of photographs of cavity and bubble formation in a tube of water at 110 mm. Hg pressure (the equivalent of 45,000 feet) after striking the bottom with a wooden block is reproduced in Figure 4.

The tensile strength of water is believed to be very high. This is demonstrated by experiments in which a slow steady pull is applied, as in those of Berthelot[15] and of Dixon,[16] where clean degassed glass tubes were completely filled with water at a high temperature and the temperature then lowered, allowing the greater differential volume contraction of water as compared to the glass vessel to develop the pull. Negative pressures (tensions) as high as 150 atmospheres were found before the liquid suddenly broke, leaving a cavity.

This experiment is quite comparable to taking a piece of paper by two opposite edges and trying directly to pull it into two halves. The necessary effort is very great. On the other hand, by grasping one edge of a piece of paper with the two hands and twisting in opposite directions, the paper can be torn in two with the greatest of ease. The same amount of energy is required in either of the two methods but the rate of application of the energy (the power) necessary by the first is enormous, by the second very small.

Since tension is the negative equivalent of pressure* (i.e., negative force per unit area), if the area is small, enormous tensions may develop. In a liquid pressures or tensions quickly become equally distributed, as illustrated by Pascal's law, but, if the tension develops

* Pressure in a gas can never become negative, but in a liquid, gel or solid high negative pressures develop if the material is subject to a pull.

in a very short time interval, inertia and viscosity of the liquid may result in local high tensions (perhaps 100–1,000 atmospheres) so that the liquid is literally torn apart.

Considerable space has been devoted to this conception since we deal in the animal body with surfaces that *can* be *torn* apart and local pulls are involved rather than the uniform conditions of the Berthelot and Dixon experiments. Working with presumably gas nucleus free apparatus we can sometimes experimentally demonstrate the formation of cavities on the end of a glass rod drawn out of water in a narrow tube when the velocity reaches about 16 meters per sec. With corn syrup the velocity can be very low because of the inability of the viscid liquid to move into the space left by the rod, and with gelatin gel only a slight movement is sufficient to form a cavity. Moreover, the weight necessary to pull a glass rod out of gelatin is only a few kilograms and the local regions of high tension can be seen as strain patterns when viewed between crossed polaroids. Gas always moves into these cavities with extraordinary rapidity and a bubble is left when the cavities collapse.

That such a mechanism must be involved in the formation of bubbles in the animal can be demonstrated in excised tissues manipulated by pulling and cutting under conditions properly controlled to insure that extraneous gas nuclei are not introduced. Connective tissue is particularly prone to form bubbles by this procedure and it is perhaps significant that the bends are associated with regions rich in connective tissue.

The Pressure Difference, ΔP

From the preceding discussion it is apparent that the tendency for bubbles to form will depend on two factors, both on gas dissolved and also on pressure in the liquid. The difference between these may be called the pressure difference, ΔP. It is numerically equal to the gas tension, t, minus the hydrostatic pressure, P. The gas tension is determined by Henry's law, which states that at equilibrium the tension of gas dissolved in a liquid is proportional to the partial pressure, p, of gas, which may be measured in atmospheres, in contact with the liquid. The hydrostatic pressure can be either positive or negative and may also be measured in atmospheres. The pressure difference, $\Delta P = t - P$, is one of the primary reasons for bubble

formation in compression-decompression and in low pressure experiments.

If a gas nucleus is present, any change in ΔP will change its volume. However, if gas nuclei are absent, the question arises as to how great ΔP must be before bubbles will form spontaneously, i.e., how much supersaturation is possible before *gas bubbles* appear *de novo* in a homogenous liquid at rest. A treatment based on thermodynamics and statistical mechanics indicates 100 to 1,000 atmospheres for spontaneous bubble formation. This is confirmed experimentally by Kenrick, Wismer and Wyatt,[17] who have demonstrated that water, if undisturbed, may be brought into equilibrium with at least 150 atmospheres of gas without forming bubbles when the pressure is released.

This statement regarding high ΔP for spontaneous bubble formation applies also to water in contact with hydrophilic surfaces whether smooth or rough and to hydrophobic surfaces if molecularly smooth but, if pitted or containing cracks, gas nuclei can form *de novo* and grow to bubbles at less than 100–1,000 atmospheres gas tension. Theoretically, if a crack or a cone shaped cavity exists with a sufficiently small angle, *de novo nucleus formation* should occur without supersaturation with gas. This *de novo nucleus* may then grow to a bubble under the conditions which control the growth of any other nucleus.

The Effect of Different Gases—Diffusion

When compared at the same tension different gases will behave alike except when rates of diffusion are important. In this case not only ΔP but diffusion constants and especially solubility must be considered. A highly soluble gas like carbon dioxide, even at a low tension, may play an important role in the early growth of a bubble by diffusion because of the high concentration of carbon dioxide molecules.

The effect is well seen when a vapor cavity is produced in a liquid by negative hydrostatic pressure. If both carbon dioxide and nitrogen are dissolved at the same tension in the liquid surrounding the cavity, they will diffuse into the cavity at rates depending on their concentrations (since the diffusion constants are nearly alike) rather than their tensions. When the vapor cavity collapses there will be a much greater proportion of carbon dioxide than of nitrogen in the bubble that persists. Later the proportion of carbon dioxide and nitro-

gen will adjust, so that at equilibrium an equal amount is present, i.e., a proportion that reflects their partial pressures.

Likewise, the size of bubbles will be greater if carbon dioxide rather than nitrogen is diffusing into them, both from the same tension. The rapid exit and entrance of carbon dioxide into bubbles is easily demonstrated by filling a long glass tube with layers of water alternately saturated with air and with carbon dioxide. The carbon dioxide layer may be colored with a dilute dye to render its boundaries visible. If minute bubbles are now produced in the air-saturated layer at bottom by striking the slightly evacuated tube a blow, the bubbles rise slowly, but when they pass into the carbon dioxide layer they jump in size, due to more rapid diffusion of carbon dioxide inward than of air out, and rise rapidly until they reach the air-saturated layer. Then carbon dioxide passes out of them rapidly; they suddenly shrink and rise slowly until the next carbon dioxide layer is encountered, when the process is repeated. We may imagine a rapid bubble growth in contracting muscle when carbon dioxide is produced, followed by the later replacement of this gas with nitrogen for permanent bubble formation.

Stability and Growth of Gas Nuclei

Gas supersaturation is like salt supersaturation, with this exception. The presence of a minute crystal of the salt is sufficient to start crystallization of the whole salt solution, whereas a gas nucleus may enlarge to a certain point in a gas supersaturated liquid but will not grow indefinitely until certain critical conditions are surpassed. The conditions are simple and clear in a sphere. The surface tension of the gas-water interface exerts an inward pressure which is inversely proportional to the radius and amounts to an extra atmosphere in a bubble in pure water of 3μ radius. This excess pressure forces the gas into solution and the bubble disappears. Small spherical bubbles cannot exist unless there is excess gas in the liquid and the conditions for stability are that $\Delta P = 2\gamma/r$, when γ is the surface tension and r the radius of the bubble.

For a gas mass sticking to a surface the conditions of stability are much complicated, since the configuration of the surface and the gas mass which may have two radii of curvature at right angles to each other, as well as the receding contact angle, which determines

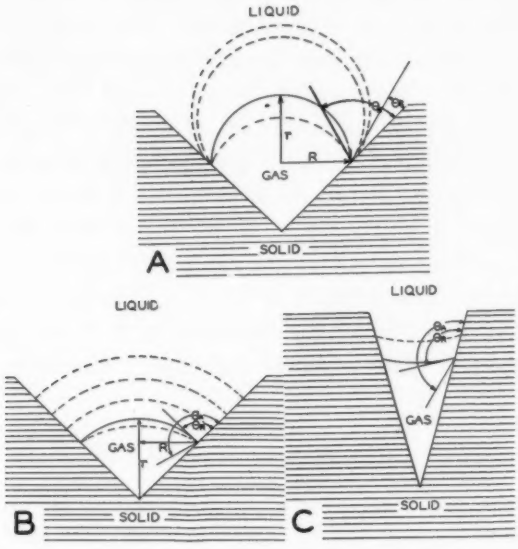

Fig. 5. A. A gas nucleus in a conical cavity of apical angle Ψ, and small receding contact angle, θ_R. θ_A, advancing contact angle. R, radius of base; r, radius of curvature of gas-water interface at moment of instability (solid line). The dotted lines show stages of growth. The hemisphere limits stability. B. A similar gas nucleus in a conical cavity with large receding contact angle which limits stability. C. A gas nucleus in a cone of acute apical angle, Ψ, so that $\theta_R > 90° + \Psi/2$. Note curvature of gas-water surface.

"creep" of the gas nucleus, are all important. It is not possible to describe in detail the conditions for stability of gas nuclei on surfaces but Figure 5 illustrates what will happen in cases which have been considered in a recent paper by Harvey et al.[18]

Wherever a surface is concave to the gas phase, as in Figure 5, C, the pressure in the gas is less than the gas tension in the water and gas would tend to move in from solution thereby continually enlarging the gas mass.

For every gas nucleus there is a certain ΔP below which it is stable and above which it grows by diffusion of gas. We may look upon a test tube of water, not especially cleaned to remove gas nuclei, as containing a population of gas nuclei of varying dimensions, each one of which will grow at a certain critical ΔP. If exhausted to one-half atmosphere, a group of bubbles will arise and then

no more appear, but on reducing the pressure to one-quarter atmosphere another group of bubbles arises. This formation then ceases but at one-eighth atmosphere another group arises and so forth. At the vapor pressure, a ΔP of $760 - 20 = 740$ mm. Hg, the hydrostatic pressure, P, has been reduced as much as possible by evacuation but by striking the tube, a pressure pulse with a tension component is set up and P becomes less than the vapor pressure, giving rise to growth of a new series of gas nuclei with the formation of more bubbles. For convenience we can call all nuclei which will grow at or above the vapor pressure of water, gas macronuclei, while those which require a greater ΔP for continued growth are gas micronuclei. The distinction is quite arbitrary and merely represents a convenient line of demarcation.

Removal of Gas Nuclei

For any experimental work with animals it is necessary to use liquids in containers or implements which have no gas nuclei sticking to them; otherwise quite erroneous conclusions may be drawn regarding the bubbling of blood, spinal fluid or tissues. Any bubbles which appear in such an experiment may have come from gas nuclei on the surgical instrument or apparatus rather than from the blood or tissue (see Harvey et al.[19]).

The first necessity for avoidance of gas nuclei is to avoid hydrophobic material. This is not because a hydrophobic surface cannot be cleaned of gas nuclei, for it can, if always under water, but because the water runs off when exposed to air, and an air film then sticks by virtue of its contact angle. The surface should be so clean that a water film will cover it *completely* when removed to the air. If container and water are then well centrifuged, macronuclei or dust particles on glass can be removed and the water will not bubble at the vapor pressure. After treatment by this method, M HCl and M $NaHCO_3$ can be mixed without bubble formation and yeast can be grown in gas-nucleus-free culture medium with copious carbon dioxide production but without formation of bubbles. Filtering may also be employed to remove gas nuclei but it is essential to make certain that no gas masses are present on the filter, for filtering sometimes introduces more nuclei than it removes.

For removal of gas micronuclei two additional methods are avail-

able, both highly effective. One removes gas from solution by prolonged boiling or evacuation, thereby allowing the nucleus to disappear by solution in gas-free liquid; the other makes use of increased hydrostatic pressure, thereby forcing the nucleus into solution. The latter method is the most convenient, since the liquid retains its previous gas tension after a high pressure treatment and the difficult task of resaturation without introducing gas nuclei is avoided. We have placed both water and container in a steel chamber filled with water, and have used a hydrostatic pressure of 16,000 lb./in.^{2} (1,090 atmospheres) for 15 to 30 minutes. Such previously compressed water in a clean glass tube has remarkable properties. It can be heated to at least 202° C. before bursting into vapor, although evaporation from the surface is enormous. When intense high frequency sound waves are passed through, no cavitation occurs and no bubbles arise. Finally, if exhausted to the vapor pressure of water at 20° C., moderate knocks have no effect and only a very severe blow, strong enough nearly to shatter the glass, will cause bubbles to form.

Although this water is gas-nucleus-free, bubbles can still be produced in it by procedures which increase ΔP to the 100 to 1,000 atmospheres necessary for spontaneous bubble formation—either by decreasing P, as when a glass rod is rapidly pulled out of the water with cavitation and bubble formation; or by increasing t, as when such water is electrolyzed and the gas concentration rapidly rises at the electrodes or when frozen and the formation of ice crystals (in which gas is insoluble) raises the gas concentration to a high value in pockets of the unfrozen liquid.

Gas Nuclei in Blood

With these fundamental principles in mind we may now turn to the animal and apply them to the observed facts. At altitude bubbles are rarely observed in resting animals but do appear in blood vessels as a result of muscle contraction, whereas in resting animals decompressed to one atmosphere from high air pressures the bubble formation is profuse in blood vessels, and many tissues are a froth of bubbles.

Since bubbles appear most readily in blood it was natural to test this liquid for gas nuclei. Previous experience with glass models and methods of removing gas nuclei have supplied the technique for drawing samples of blood into a long clean wet glass tube, or pompholy-

gometer, one end of which is a cannula inserted and tied in the blood vessel. By appropriate clamps, stop-cocks and connections to a vacuum reservoir, successive samples of blood in the pompholygometer can be tested below the blood vapor pressure at 38° C. to see if gas nuclei are present which will grow into visible bubbles. The testing conditions of less than 47 mm. Hg are equivalent to an altitude of 63,000 feet (a ΔP of 713 mm.), far greater than the animal itself can stand.

The carotid blood when sampled in the above manner has been found to be free of gas nuclei in resting cats at ground level as well as in cats after a previous exposure to high altitude.* Even when the blood is drawn at an altitude of 45,000 feet or during a prolonged exposure to an air pressure of 100 lb./in.^{2}, bubbles have not appeared at the vapor pressure except in a few instances where contamination was suspected. These experiments indicate that all the formed elements of the blood (red and white corpuscles, platelets, fat globules or blood dust) play no part in bubble formation, that air masses do not normally pass from alveoli to lung capillaries (although they may when the alveolar air pressure is raised above that in the capillaries) and that movement of the blood with turbulence and vortex formation around the valves of the heart does not normally start bubble formation. They lead to the conclusion that bubbles must arise from gas nuclei sticking to or formed on or within the endothelial linings of the vascular system or extravascular spaces and only when they have enlarged to the point of instability do they pass into the blood stream.

A few attempts were made to sample venous blood from the postcava below the renal vein, but the low blood pressure and the tendency for this vessel to pass into spasm has introduced difficulties. These can be overcome but the postcaval wall is so thin that bubbles within can be readily seen with the naked eye. The postcava, in fact, is a natural pompholygometer for testing blood from the hind quarters of the body and has been used in our standard experimental procedure in studying bubble formation.

Animal Technique

The cat is anesthetized with nembutal and the abdomen opened with little loss of blood. The viscera are pushed aside and covered with moist cotton to prevent evaporation, thereby exposing a considerable

* The word altitude used in this sense throughout this paper refers to a simulated altitude in a low pressure chamber.

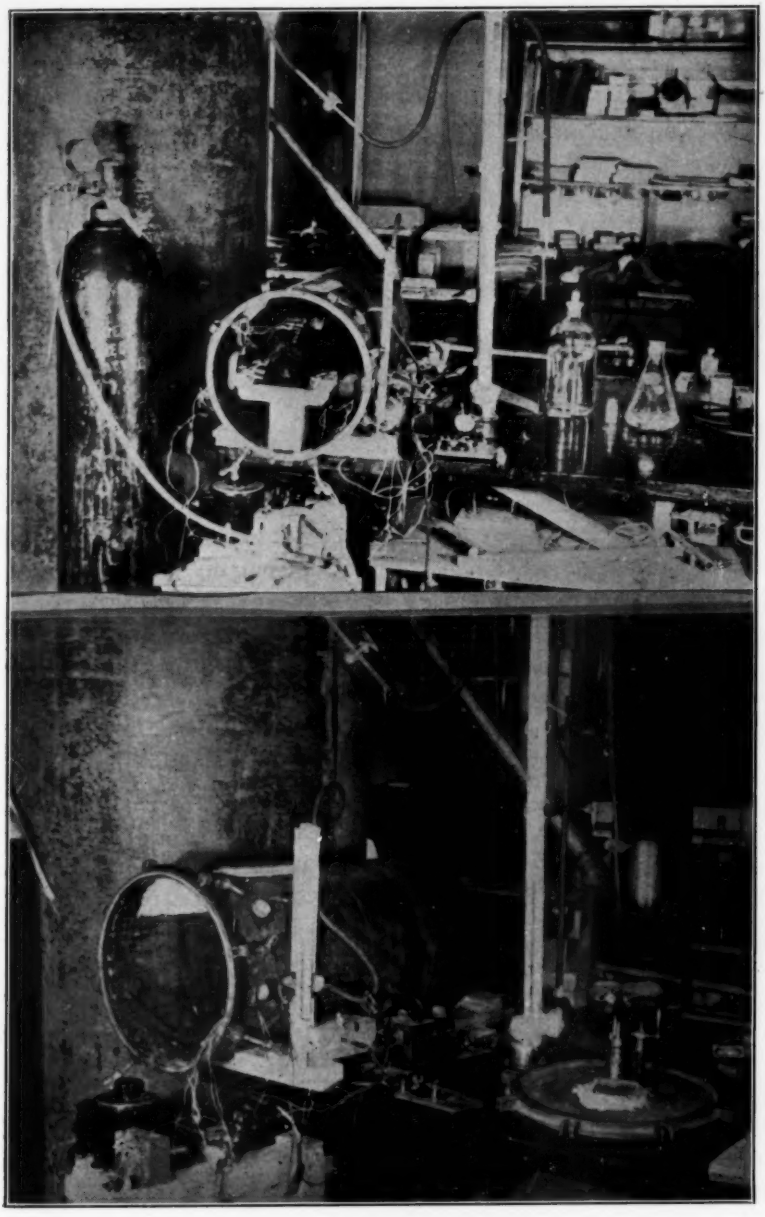

Fig. 6. Above—View of high altitude chamber with cat in position, reservoir vacuum tank for rapid removal of air from altitude chamber, oxygen cylinder, mercury altitude gauge and accessory apparatus. Below—Near view of same, showing mercury blood pressure manometer on outside of altitude chamber. Equalization of pressure is effected by connecting open end with interior of chamber.

length of the postcava together with its tributary branches. When the cat is placed in a horizontal position in the altitude chamber and well illuminated, observations can be readily made through the glass observation ports, and bubbles of 0.2 mm. diameter can be seen within the veins. Only when bubbles are very large can they be detected in arteries.

The altitude chamber, shown in Figure 6, is an old autoclave, connected by a good-sized pipe and valve to a large reservoir chamber which can be evacuated with an air pump. The capacity is such that by opening the valve quickly or slowly the small chamber reaches the simulated altitude at any desired rate from explosive decompression to our usual average "rate of climb" of 5,000 feet per second.

The chamber is too small to admit a man and the altitudes are often so high that no man could exist for any length of time. Therefore, various devices have been developed for physiological manipulation from without the chamber. Some of these devices are shown in Figure 7. Blood pressure can be determined with a carotid cannula inside and a mercury manometer outside the chamber, provided care is taken to remove gas nuclei from connecting tubes. The open end of the manometer is reconnected to the altitude chamber for equalization of pressure as shown in the lower portion of Figure 6. Electromagnetic clamps for blood vessels or tracheae have been devised that will either open or close on making a contact, as well as automatic syringe for injecting solutions. Finally, an ingenious "mouse trap sectioner" for cutting the spinal cord with the cat in the chamber is activated by electromagnetic release of the spring of the trap to which a wire is attached that cuts through the cord.

Pure oxygen is administered by a glass tube fitting loosely over a tracheal cannula. The altitude has been mostly 45,000 feet (110 mm. Hg), selected as a convenient high level at which cats would live for at least an hour with oxygen breathing despite considerable anoxemia. Under these conditions the rate and extent of bubble growth would be as great as possible.

Resting Animals at Altitude

If a series of resting nembutal anesthetized cats are prepared in this manner and observed for at least an hour at 45,000 feet, bubbles rarely appear in the postcava. Even at 50,000 feet where a percentage of the

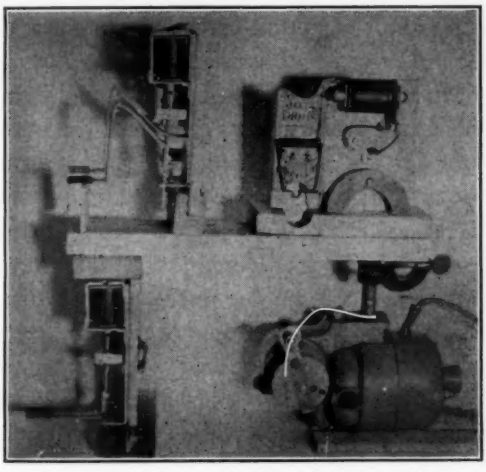

Fig. 7. Various devices for manipulation in tank. Upper left—artery clamp closed by electromagnet. Lower left—artery clamp opened by electromagnet. Upper right—mouse trap spinal cord cutter. Lower right—motor and eccentric for passive movement of leg.

animals die, bubbles are not usually found during a 60-minute observation or during the life of the cat. Since dissolved gas in the animal is constantly and rapidly lost at this altitude by the efficient breathing and circulatory mechanisms, aided by further compensatory changes resulting from anoxemia, experiments were undertaken to retain the dissolved gas, expecting that bubbles might then appear. Both arteries (aorta and collateral arteries) and veins (postcava) were tied, or the leg was tournaquetted or the trachea clamped (when the heart continues to beat for 6-8 minutes), but even under these more favorable conditions, bubbles failed to appear.

Animals Stimulated at Altitude

However, if the hind legs of the cat were stimulated vigorously, bubbles from limb veins could be observed moving up the postcava, sometimes within 5 seconds of stimulation. By 16 minutes the great majority of the animals had formed bubbles although there was variation in time of appearance from cat to cat and an occasional animal was resistant to bubble formation and remained free of them despite this procedure. If only one leg was stimulated, the bubbles formed in

that leg and appeared in veins draining that leg only. This important discovery of the effect of muscle contraction on appearance of bubbles was first made by Whitaker, Blinks and collaborators,* using bullfrogs, and has its practical application in the well recognized fact that straining movements and exercise among aviators is the most important predisposing factor for the development of bends and chokes.

Another point of special interest is the variability in time of bubble formation in cats, which has its counterpart also in the varying resistance and susceptibility to decompression sickness observed in men. Part of this variability may be due to force and extent of muscle contraction on stimulation, part to differences in the circulation and part to the fat content of the animals, for it is well recognized that fat men are particularly susceptible to bends after diving and Boycott and Damant[8] found a correlation between fat content and bends in goats after an exposure to compressed air. Since nitrogen is about five times more soluble in fat than in water, a large volume of gas is available for growth of bubbles in fatty regions.

To test the effect of fat content and bubble formation at altitude, the fat of the subcutaneous region below the diaphragm (including the inguinal fat pads and deposits below the skin of the legs as well as the popliteal space) was removed from more than 400 cats, weighed and then expressed as a percentage of the body weight. When time of bubble appearance was plotted vs. fat content, no correlation could be detected, a result we believe to be connected with the rather rapid appearance of bubbles after the muscles are stimulated. Only when the bubble formation is relatively slow, as on decompression from critical excess air pressures, have we observed a correlation between time of bubble production and fat. It is under these conditions that the slow seeping of additional nitrogen from fat deposits can make itself felt. Fat does not appear to be a primary cause of variability.

If stimulation of the hind legs is made at 35,000 feet (180 mm. Hg) bubbles also appear but they are smaller and often hard to see. At lower altitudes we may expect to find minute bubbles of microscopic dimensions too small to do any harm.

Animals Stimulated Before Ascent

Evidently stimulation of the legs at altitude increases the ΔP above

* Private communication.

that due to the altitude itself, so that bubbles appear in consequence. Such an increase in ΔP must enlarge gas nuclei even at ground level, and it is conceivable that the enlarged nuclei might persist for a sufficient time to give rise to bubbles if the animals were subsequently exposed to high altitude. We have a comparable experiment in a glass tube filled with water and free of any gas nuclei that can grow to visible bubble size at 45,000 feet (110 mm. Hg). If the tube is hit a few blows at ground level, no bubbles may be visible but when immediately evacuated to 110 mm. Hg, bubbles appear. If there is a delay before evacuation the gas nuclei disappear and bubbles will not form.

The analogous experiment succeeds in the animal. When the hind legs of cats were stimulated once a second for twenty seconds and the animals immediately taken to 45,000 feet, bubbles appeared in seven out of ten cats. However, if there was a wait of ten minutes before ascent to 45,000 feet, in only two of ten cats did bubbles appear. During this wait the enlarged gas nuclei in the animals had returned to their original condition. It is therefore apparent that vigorous muscle contraction and straining movements should not be carried out just before ascent, because, due to the excess ΔP, gas nuclei will be enlarged and may form bubbles at the altitude.

On the other hand, muscular exercise must have a beneficial effect in preventing bubble formation by virtue of the marked vasodilation and opening of closed capillaries in muscle tissue as well as the increased circulation and hyperventilation necessary rapidly to remove carbon dioxide from the blood. During exercise exactly those physiological mechanisms, naturally designed to remove a gas (carbon dioxide), are brought into play and they may be just as efficient in removing a gas such as nitrogen which is necessary for permanent bubble formation. The relative influence of these two opposing factors—the enlargement of gas nuclei by muscle contraction, and the increased gas elimination due to similar activity—will determine how much and how strenuous the exercise can be.

Actually, experience has shown that in man pre-exercise at ground level before ascent, even when combined with oxygen breathing, is not as beneficial as might be expected and little increase of protection is afforded over inhalation of pure oxygen at rest unless the exercise ceases some time before ascent. Moreover, the hyperventilation and additional oxygen required to make up the oxygen debt imposes an

excessive strain on the present oxygen mask and breathing equipment. In cats prestimulation with continued stimulation during ascent and at altitude does so increase the circulation and accelerate removal of nitrogen that visible bubbles are rarely observed in their blood.

In decompression after deep diving or other work under pressure, exercise has been advocated as a ready and efficient means of accelerating the removal of nitrogen. There are in fact reasons why this increase in ΔP from exercise is much less effective at ground level than at high altitude, reasons bound up with the mechanism of bubble formation during muscle contraction.

Mechanism of Bubble Formation After Muscle Contraction

It is obvious that an increase in ΔP, which we have defined as the gas tension, t, minus the hydrostatic pressure, P, may result either from an increased gas production or a decreased hydrostatic pressure, due to stretching of the liquid, i.e., to mechanical tension. Both factors are involved in muscle activity, the excess carbon dioxide and the mechanical tension of contraction. One of these factors, the decreased P, becomes particularly important at altitude because the animal is already near the vapor pressure of water (47 mm. Hg) and the mechanical tension of muscle contraction may expand a gas nucleus to a large vapor cavity such as is shown in Figure 4. Dissolved gases would diffuse into this cavity at a rate depending on their relative concentrations and diffusion coefficients and the surface area of the cavity. The larger the vapor cavity, and the longer it persists before collapse, the larger will be the resultant bubbles. In previously air pressure treated cats at one atmosphere, with the same mechanical tension developed by muscle contraction, the decreased pressure may not reach the vapor pressure or may be only slightly below the vapor pressure so that a vapor cavity would be small and its persistence short. In this case the gas diffusing into the cavity would be far less; bubbles would be small and take more time to reach a visible size. In either pressure exposed animals or those at altitude, the high concentration of newly formed carbon dioxide from muscle contraction must greatly accelerate the early growth of bubbles.

Our conception of the mechanism of bubble formation during muscle contraction emphasizes both carbon dioxide concentration and mechanical tension, but, if the above reasoning is correct, the facts

point to mechanical tension as the more important of the two factors. Additional evidence in favor of mechanical tension comes from two types of experiment. In one, the legs of cats have been stretched without active muscle contraction and hence without carbon dioxide production, and in a second, lactic acid was injected so as to increase carbon dioxide without the mechanical tension. In a third type of experiment the muscles of the legs have been crushed and injured. The crushing must itself exert a mechanical tension on muscle fibers as well as mechanically stimulate them locally, with carbon dioxide production and acid of injury. Although its bearing on the theory of bubble formation during muscle contraction is not so clear cut, it has turned out to be a most effective method of inducing bubble formation. These three types of experiment may now be considered.

Crushed and Injured Tissues

The first experiments on injured tissues were carried out by striking the thigh muscles of the anesthetized cat with a rubber hammer so as not to puncture the skin but to bruise and break small vessels, causing extravasation of blood in muscle tissue. The animals were then immediately taken to 45,000 feet altitude and in nine out of ten cats bubbles appeared in the postcava.

The blows might have resulted in bubble formation by setting up a series of pressure pulses as in the glass tube experiments previously described (p. 515). Therefore a crushing device was constructed for slowly squeezing the thigh muscles and actually tearing them, but without perforation of the skin, which might allow air to enter from outside. Again, when the cats so treated were taken to 45,000 feet, either immediately or after a wait of 10 minutes at ground level, the bubble formation was profuse. Bubbles could also be found locally in the injured region. These experiments indicate that bubbles might readily form and pass into the circulation of injured men at a high altitude.

The crushing procedure is such that very strong stretching forces are exerted on the muscle fibers, sufficient in some cases to actually break them transversely. This mechanical pull must play an important part in the bubble production, for it can be shown that injury to tissue containing no striated muscle is ineffective in forming bubbles, even when the volume of tissue injured is greater than in the muscle injury experiments. Thus, stripping the intestines, squeezing the kidney to a

pulp within its capsule, crushing the testes or bruising large areas of the skin have all failed to result in bubble formation when the cats were observed at 45,000 feet. Acid of injury and carbon dioxide must be formed in these tissues also (although possibly not in such high concentration as in muscle) so that the mechanical tension developed in crushing the muscle tissue would appear to be the important factor in formation of bubbles during muscle injury.

Passive Movement and Stretching

Passive movement of a leg can be attained by attaching the foot to an eccentric run by a motor, so that the leg is rapidly moved back and forth. Movement of this sort at an altitude of 45,000 feet does not give rise to bubbles. However, if a wire is attached to the ankle of a resting anesthetized cat, securely tied to its operating board, and the leg vigorously stretched at 45,000 feet, bubbles will appear, provided the blood supply to the leg is cut off by clamping arteries and veins. Without the vessel clamping, removal of gases by blood flow is sufficiently rapid to prevent bubble formation. Since the clamping of arteries and veins does not give rise to bubble formation without stretching, it appears probable that the mechanical tension is the cause of the bubbles.

Lactic Acid Injection

Any local increase in lactic acid should liberate carbon dioxide from blood and imitate the excess carbon dioxide produced on muscle contraction. Therefore gas nucleus-free lactic acid was injected into the aorta, usually under conditions (clamping of proper vessels) that prevented its rapid removal by the circulation but insured its distribution to the hind quarters of the cat. These experiments have been carried out, both on cats previously exposed to air pressures of a critical value and duration (3.5 atmospheres for 2 hr.) such that bubbles ordinarily appear only a considerable time after decompression, and also in cats at an altitude of 45,000 feet.

In the cats exposed to compressed air collateral vessels were not clamped. The injection was made immediately after decompression and no bubbles were observed. In the "altitude" cats, injection was made just before a rapid ascent to 45,000 feet. In these animals bubbles appeared in nine out of twenty-one animals whereas in a control series injected with gas nucleus-free saline solution only one out of ten formed

bubbles. The difference is not significant when analyzed by the method of Chi square, but there is perhaps a trend, a tendency for lactic acid to favor bubbles, but not nearly as significant as the effect of muscle contraction itself. These experiments, combined with the leg stretching experiments, indicate that mechanical tension must be the predominant factor in the formation of bubbles.

Composition of Bubbles in Blood

Analyses of gas bubbles in blood by the ordinary methods indicate a very high percentage of nitrogen. They have been considered nitrogen bubbles for all practical purposes. This is what might be expected from the tensions of gases at equilibrium in blood. However, when gas moves into a bubble rapidly, particularly into a rapidly forming vapor cavity, the composition of the gas left after collapse will depend mostly on the concentration of gas dissolved in the surrounding liquid, i.e., its solubility as at a given tension. Highly soluble carbon dioxide must be present in excess. If the bubbles could be obtained and analyzed while very small the carbon dioxide content would undoubtedly be high. This excess carbon dioxide must pass out of the bubble again and the final composition depend on gas tension rather than concentration. Therefore, in the early growth of a gas nucleus carbon dioxide may be very important, but for bubble persistence the nitrogen tension, represented by a partial gas pressure, is the determining factor.

When an animal breathes pure oxygen the nitrogen is flushed out of the body, but the carbon dioxide, which is a body product, remains at practically its original level. Carbon dioxide is also constant in an animal exposed to high air pressure, which dissolves an excess of nitrogen but the increased carbon dioxide pressure in the compressed air is small compared to the carbon dioxide produced by the body. Oxygen is always so rapidly used by the body that its tension is kept relatively low. Nitrogen becomes the important gas for permanent bubble formation and its removal essential.

The Effect of Oxygen Breathing

It is therefore not surprising to find that oxygen breathing for a sufficient time before ascent will completely prevent the formation of visible bubbles in the postcava of cats after vigorous stimulation of the hind legs. The actual time of oxygen breathing depends on the

strength of contraction. With our standard 17-volt, 60-cycle, A.C. stimulus, one hour is sufficient to protect half the cats but one-half hour is not nearly enough. If the stimulus is reduced to 6 volts, resulting in a less vigorous muscle contraction, the cats are fully protected after one-half hour of oxygen breathing.

A weak stimulus will result in the development of a lower tension, both locally, due to fewer fibers pulling together at one spot, and generally, due to fewer muscles coming into play. The end result is reduced hydrostatic pressure, which does not give a sufficient ΔP for bubble formation at the low nitrogen tension existing after one-half hour of breathing oxygen. The greater number of muscle fibers contracting after strong stimulation will produce more carbon dioxide but because of the circulatory adjustments bound up with excess carbon dioxide production, the concentration of this gas will not rise proportionally. The decreased hydrostatic pressure due to mechanical tension again appears to be more important than the carbon dioxide. After one-half to one hour of oxygen breathing the nitrogen tension in the postcaval blood of cats is very low so that only gas in the most inaccessible and poorly vascularized places can be involved in bubble production.

In man also, oxygen breathing before ascent will completely prevent the appearance of all symptoms of decompression sickness, and offers the most effective prophylactic treatment. In man, the amount of oxygen breathing necessary has also been shown to depend on the extent of exercise at altitude. The actual time of oxygen breathing to prevent bends in man and to prevent bubble formation in the blood of cats is about the same.

Moreover, a comparison of nitrogen elimination curves from analysis of nitrogen tension in veins and arteries of man and cat show a surprising similarity in the actual time relations, despite the huge difference in volume of man and cat (30: 1). In both animals also, the rate of nitrogen elimination during exercise is greatly increased. The circulatory systems of man and cat appear to be so adapted that in man oxygen can be supplied and waste removed in approximately the same time as in the cat, despite the difference in volume of tissue to be serviced. This adaptive relation is probably widespread among mammals of different mass and is no doubt connected with some basic property of cells, perhaps the time that certain cells can withstand lack of oxygen or the accumulation of injurious metabolites.

The Effect of Circulatory and Respiratory Changes

We have already seen that the circulatory and respiratory changes of exercise are perfectly adapted for rapid removal of gases but at the same time the muscle contraction of exercise, even at ground level, is an effective producer of bubbles. Some other method of increasing the circulation would be desirable to reduce the incidence of bends.

One, the use of drugs has not been thoroughly tested in the cat. Another, lack of oxygen, cannot be successfully applied to man but experimentally, in the cat, has turned out to be a fairly efficient method of reducing the bubble formation. When oxygen is withheld from the animals at 45,000 feet for some minutes before stimulation is begun, there is a significant difference in the number of cats in which bubbles appear, as compared with a control series receiving oxygen continuously. The hyperventilation of these anoxemic animals is observed to be marked and we may presume that accompanying the hyperventilation there is the usual reflex vasodilation designed to supply muscle tissue with all the oxygen available. At the same time nitrogen is effectively removed.

The Site of Bubble Formation

The wide variety of decompression sickness symptoms has led to the view that bubbles may form in almost any part of the body, and indeed, after an extreme compressed air treatment, bubbles are found in all regions of a cat, including arteries and veins, lymph vessels, eye humors and amniotic fluid, although not in the bladder urine. They are very abundant in fatty tissue and can be seen in veins draining fat deposits.

We have not determined whether these bubbles, which are abundant in the viscera, ever occur *within** the cells of the body but this is very unlikely. All attempts to detect bubble formation within single living uninjured cells (such as Paramecia, Amoeba, Nitella, sea urchin or starfish eggs) have failed. In some experiments the cells were saturated at a nitrogen pressure as high as 2,300 lb./in.^{2} and then decompressed. The outer surface of the cells was observed to act as a source of bubbles, but they never formed within, unless the cell was injured or dead. It is therefore doubtful that bubbles form within mammalian cells

* Gersh[29] has described bubbles within fat cells from guinea pigs (previously exposed to air-pressure treatment), examined in sections prepared by the rapid-freezing technique.

but they probably appear in intercellular spaces and would be most likely to form where one surface can be pulled away from another.

In cats at an altitude of 45,000 feet, bubbles, after stimulation, are confined to the blood vessels and occasionally appear in lymph vessels. They are mostly found in veins, probably due to the lower blood pressure and greater gas tension (and hence lower ΔP) as well as direction of flow. Bubbles have never been observed in eye humors, urine or amniotic fluid, nor have they been observed around joints, although examination could not be made at altitude. At ground level this gas may have contracted to so small a volume as to escape detection.

In man numerous X-ray studies made in altitude chambers have disclosed the presence of air masses in joint cavities, in popliteal fat and in the fascia between muscles. All observers agree that air may be present in these regions without the pain of bends. It has also been observed that fluid can be injected into the bursa without giving rise to discomfort and gas in the bursa itself is not correlated with pain. Statistically, gas in popliteal fat and muscle fascia appears most likely to cause pain and we are led to the view that the undue expansion of gas in critical sensitive regions of connective tissue* stimulates sensory endings of pain nerves. Since localization of pain is not usually precise, it is frequently referred to the joint.

Another theory of bends pain refers it to the pain of muscle contraction in absence of oxygen, described by Sir Thomas Lewis.[21] Bubbles blocking the blood flow through muscle (true aeroembolism) would prevent access of oxygen and initiate conditions for the pain of anoxic contraction. However, the above mentioned X-ray photographs do not with certainty reveal bubbles caught in blood vessels. This fact, together with the observation that local pressure application or even a blocking of the blood flow by tourniquet above the painful region (which may also increase pressure by blocking venous return) will relieve bends, are both contrary to the intravascular embolism theory. They favor extravascular gas as the cause of bends pain.

Tension must be involved in gas formation in joints. Even at ground level some persons can develop gas in the shoulder joint by a proper rotary motion of the arm that puts strain on the shoulder. By a sudden pull on the fingers also, gas will appear in the finger joint as demon-

* Dr. A. C. Ivy informs me that he has a number of cases of bends where no gas could be detected in the roentgenograms.

strated by Nordheim.[22] At high altitude the formation of gas under such conditions will be greatly facilitated.

It is impossible, from examination of the chest by roentgenogram, to distinguish excess gas in blood vessels from air in lung alveoli but several cases of chokes have shown an enlargement of the right heart which could be due to gas blocking the normal blood flow.* As shown by Van Allen, Hrdina and Clark[23] and confirmed by our work on the cat, bubbles do not ordinarily pass the lung capillaries, due to the low pulmonary blood pressure, although they are able to pass systemic capillaries. We have frequently observed the heart of a cat to be distended with air from a rather copious bubble formation in veins when no bubbles could be found in arteries. It seems highly probable that air collecting in pulmonary capillaries could give rise to those sensations characteristic of the chokes.

Nervous symptoms are more difficult to analyze. They could be due to gas blocking capillaries of the central nervous system or to gas in nerve sheaths exerting pressure on nerve trunks. We do not know. Skin effects are also puzzling. Local bubbles in the skin have not been demonstrated. Frequently the skin rash will be distributed in a cutaneous area supplied by one sensory trunk, like the dermatone areas of herpes zoster. Possibly skin rashes, as well as the local anesthesias and hyperesthesias, are the result of nerve blockage, either central or peripheral. Some details remain to be filled in but on the whole the etiology of decompression sickness can best be expressed by one word—bubbles.

* Private communication from Dr. Ivy.

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THE THERAPY OF LIVER DISEASES*

CHARLES L. HOAGLAND

Associate Member, The Rockefeller Institute for Medical Research

IF WE CONSIDER the many clinical syndromes which may be accompanied by various degrees of depression of hepatic function, it is apparent that the afflictions of the liver are almost as numerous and diverse as its multiple functions. In addition to a variety of diseases which affect primarily the hepatic parenchyma or associated biliary channels, there is a large group of metabolic, endocrine, and infectious diseases in which the major symptoms are referable to other organs, but which are often accompanied by marked alteration in hepatic function. Fortunately, the regenerative capacity of the liver is sufficiently great that few of the processes which produce alteration of hepatic function result in irreversible pathologic changes in the liver. A mere recitation and superficial description of the diseases which have been shown by clinical chemical methods to affect the liver adversely would require more time than has been made available for this presentation. The discussion will, therefore, be limited principally to a consideration of the most important organic non-surgical and non-malignant diseases of the liver, with particular attention given to current theories of basic therapy which may be employed in the treatment of these disorders. Some attention will be given at the same time to those aspects of the physiology and pathology of the liver which provide the rationale for current types of therapy. It should be emphasized at the outset, however, that in view of the extraordinary speed with which new information concerning the metabolic events occurring in the liver is being supplied from laboratories devoted to basic physiological research on this organ, any plan of therapy presented at this time must be modified and kept constantly in line with these advances.

A discussion of the problems posed by the therapy of non-obstructive, non-malignant diseases of the liver may be preceded by a statement concerning the general problems presented by those diseases which are

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characterized pathologically by destruction of the hepatic parenchyma. Actually, until we are better informed concerning the nature of the various etiological factors at work in liver disease, we accomplish most in therapy by devoting our attention chiefly toward those measures which hasten repair of the damaged liver, regardless of the nature of the agent or process initiating the disorder. In obstructive lesions of the biliary channels or in affections of the gall bladder, attention is naturally focussed on the nature of the inciting agent, often with an eye towards its surgical removal. Here, too, owing to the fact that the parenchyma of the liver rarely escapes some degree of associated damage, the alert surgeon has come to pay increasing attention to the problem of hepatic reserve, and to those factors which accelerate regeneration of liver tissue.

The last decade has been particularly fruitful in providing information on the multiple factors which make for the maintenance of optimal liver function and on the agents which stimulate growth and repair of the liver parenchyma following experimental damage to the liver. A rational plan of therapy for the liver diseases will, therefore, fall short of the ideal in so far as it neglects to take into full account pertinent information in the fields of nutrition, physiology, and biochemistry, which has been made available within the last few years.

Since chronic liver diseases stem from preceding acute processes in the liver, it would seem wise to preface a discussion of the treatment of chronic liver disease by a brief account of the medical management of acute hepatitis. Strictly speaking, the term "hepatitis" is applicable to all syndromes which arise as a result of damage to the tissues of the liver, whether the provoking agent be chemical, physical, bacterial or viral in nature. According to some workers, the term hepatitis should also cover not only the degenerative changes which occur in the organ as a result of the action of these agents, but the reactive and reparative phenomena as well.[1] As subdivisions under this classification, one may place the various forms of hepatitis, such as acute, sub-acute, chronic and suppurative. A classification has been devised by Bloomfield[2] which depicts the various subdivisions in this scheme in a most graphic manner (see accompanying diagram). The classification proposed by Bloomfield is particularly useful in enabling the clinician to keep in mind the underlying sequence of phenomena in hepatitis, and to aid him in avoiding confusion from the older terminology. In Bloomfield's

scheme the variations which may occur in the course of hepatitis are represented by: (1) Acute hepatitis progressing rapidly to death. In older terminology this would be referred to as acute yellow atrophy. (2) Acute hepatitis with apparent recovery, but with actual transition to a latent stage, with or without remissions. If clinical recovery does not follow, this may develop into a fibrotic stage, which is commonly referred to as cirrhosis. The third, and remaining group is composed of those cases in which hepatitis is latent from the start, and is masked clinically until incipient liver insufficiency supervenes. The analogy of this classification to that which has been devised for diseases of the kidney is immediately apparent. It may be recalled in this connection that until a coherent and simple classification had been devised for affections of the kidney, rational plans for the management of kidney disorders were largely defeated by a chaos of speculation regarding the nature and site of the pathological lesions. In the development of effective therapy for cardiac diseases, cardiologists have learned long ago to keep an attentive eye on the physiological status of the myocardium, and to disregard for the immediate purposes of treatment the primary etiologic factors in these diseases. The liver, like other glandular organs, has only a limited number of ways to respond to a large number of injurious agents and phenomena, and there is no valid reason to assume that the resulting pathology, except in a few reasonably clear-cut instances of liver disease, such as yellow fever, chronic passive congestion, etc., bears any distinctive etiologic label. There is even less evidence that the resulting type of metabolic disturbance bears any relation to the initial inciting process. Therapy, therefore, in non-surgical lesions of the liver should be concerned mainly with hepatitis, and the type of therapy dictated largely by a consideration of the *stage* of the hepatitis, i.e., whether it be acute, sub-acute, or chronic in its clinical manifestations.

The primary factors of importance in the therapy of hepatitis in its acute stages can perhaps best be illustrated by a consideration of the disease, infectious hepatitis. There have been few wars during the past century in which infectious hepatitis, or epidemic jaundice, as it is commonly called, has not been responsible for a significant portion of the total illness of troops not arising directly from injuries sustained as a consequence of participation in combat.[3, 4] During the present war, epidemic hepatitis has assumed even greater importance, and although the

exact number of cases among all the combatant forces of the world has not yet been revealed, there is sufficient evidence from published reports already available to lead us to believe that it is one of the more important non-combatant causes of morbidity among troops of all branches of the military service.[5]

Epidemic jaundice, however, is by no means limited to members of the fighting forces. It has been a common disease in sporadic and endemic form among young adults in civilian communities for many decades. Boarding schools, educational institutions, orphanages, and other eleemosynary institutions, have been particularly favored as sites for outbreaks of infectious hepatitis, as numerous reports from this country and England testify.[6, 7, 8] During the winter of 1921-22, the State of New York was visited over a very wide area by so-called infectious jaundice, with one report alone recording over 700 cases.[9]

The infective nature of epidemic jaundice has been clearly recognized for many years. Unquestionably the largest experiment of its kind attesting to the transmissible nature of infectious hepatitis grew quite accidentally out of an extensive program of immunization of members of the armed forces of the United States against yellow fever, with a vaccine made from chick embryo, to which a quantity of pooled human sera had been added.[10] Several recent communications deal with transmission of a disease indistinguishable clinically and pathologically from infectious hepatitis following transfusions of blood and plasma,[11] and following the use of human plasma in an epidemic of mumps.[12]

The once familiar syndrome of "catarrhal jaundice" is now regarded as identical with acute infectious hepatitis. Much of the confusion regarding this disease entity grew out of an uncritical acceptance of the original concept of acute infectious jaundice advanced by Bamberger in 1855, and strongly championed by Virchow in the decade thereafter.[5] This theory held that the initial lesion in catarrhal jaundice was a duodenitis, in some instances characterized by a mucus plug at the ampulla of Vater, followed by a spread of "catarrh" to the bile ducts with the subsequent obstruction of the biliary radicles. That the disease is one involving chiefly the parenchyma of the liver there is no longer any doubt.[13] It would appear that failure on the part of older pathologists to find primary involvement of hepatic cells in this disease was due mainly to their having been denied an opportunity to examine the liver during the acute stages.

Qualitatively the clinical features of the average case of infectious hepatitis are remarkably constant. There are, however, marked differences in the degree of severity of symptoms, ranging all the way from slight indisposition and malaise in some patients to a state of marked prostration in the exceptional case, not unlike that seen in acute yellow atrophy. In the majority of cases, a prodromal period lasting from 1 to 9 days precedes the appearance of jaundice. Occasionally it is longer, and in rare cases the prodromal period may occupy a period of 20-25 days. About 10 per cent of cases give jaundice as the presenting symptom with no other preceding clinical signs. In most cases, however, there is a well-defined prodromal stage characterized by lassitude and fatigue, nausea and almost complete anorexia. Frequently there are complaints of epigastric pain, but only rarely of pain in the upper right quadrant. Liver enlargement is present at some stage of the disease in nearly all cases showing moderate to severe icterus. The appearance of bile in the urine is observed by the patient in nearly every instance within a period of one to three days before the appearance of jaundice in the sclerae. Less frequently the patient will also have noted light or clay-colored stools during this period. Frank recrudescence of the disease, a state recognized by deterioration of the patient's condition during recovery, and leading to a return of clinical symptoms, may occur in the exceptional case.

A study of the metabolism and liver function in infectious hepatitis reveals extraordinary aberrations in almost all biochemical and physiological systems for which there are adequate tests. Except in the infrequent case presenting signs of chronic liver disease, all abnormal values for the various constituents of the blood and urine in patients with infectious hepatitis return to a normal range within 30 to 40 days. Numerous tests, covering a wide and diverse range of liver functions, have been applied to a study of this disease by many investigators. A consideration of the results obtained by various workers reveals a surprising correlation in the degrees of alteration shown by the various tests at any time during the course of the disease in any given case. In a consideration of the average case, it is hard to escape the conviction that the principal damage to the liver consequent to this disease occurs early, and that during the major part of the patient's illness we are observing only a sequence of phenomena having to do with regeneration of the liver parenchyma.

Therapy of Infectious Hepatitis

Except in the occasional case, when the disease becomes chronic, or in the rare case which terminates fatally, infectious hepatitis is a self-limited disease. Spontaneous recovery, in so far as it can be detected by clinical or laboratory means, occurs in the majority of cases within 30 to 40 days after the onset of initial symptoms. Until more specific information is at hand concerning the infectious nature of this disease, we are forced to limit our attempts at therapy to those measures which are believed to hasten repair of the damaged liver. Lack of specific information concerning a rational therapy for infectious hepatitis, however, has not prevented the development of very fixed notions regarding therapeutic regimes; and the literature, including textbooks devoted to treatment, abound with specific guides often diametrically opposed in substance and character for the management of the acutely damaged liver. According to some schools of thought, all forms of fat are to be avoided. At the same time, a diet high in protein is strongly recommended. The dietitian who is able to plan a diet high in biologically active protein without at the same time including a liberal quantity of fat deserves more commendation for her ingenuity than for her consideration of the patient's appetite. Until adequate experimental evidence can be adduced showing that diets which contain a moderate amount of fat are injurious to patients with acute non-obstructive disease of the liver, it seems unwise to prescribe diets which provide as little as 25 grams of fat daily. Anorexia is often a troublesome factor in the management of the patient in the acute stages of infectious hepatitis. Diets which are largely free of fat contribute further to the anorexia, since they are particularly unappetizing. They are also low in calories and in fat-soluble vitamins in relation to their bulk. The dictum against the inclusion of fats in the diets of patients with infectious jaundice doubtless arose from a mistaken concept of the pathology in this disease. While obstruction of the finer biliary radicles may occur, the disease is one which affects primarily the hepatic parenchyma and not the major bile passages, as claimed by Virchow. Evidence that a diet high in fat may not be desirable in the management of the damaged liver is based on results with experimental animals in which it is claimed that liver regeneration and survival of the animals is hindered by the inclusion of large quantities of fat in the diet.[14, 15] There is no good evidence, how-

ever, that inclusion of moderate amounts of fat is harmful if an adequate intake of protein and carbohydrate are provided at the same time.

That a diet high in protein is optimum for hastening repair of the liver is not universally admitted. There are reports, notably those of Mann and collaborators[16] in which it is claimed that in the dog, liver regeneration is delayed by the administration of a diet high in protein. Recent experiments of Whipple and collaborators,[17] however, in experiments on the regeneration of the liver after damage from chloroform, appear to have laid the ghost of diets low in protein, in the treatment of liver disease. All workers seem to agree on the value of a diet high in carbohydrate. Not only are diets high in carbohydrate indicated on the basis of the protective value of such diets against liver intoxication, but on a physiological basis as well. Widespread damage to the parenchyma of the liver may be accompanied by hypoglycemia, owing to low glycogen reserve. In these cases a high intake in carbohydrate may be necessary in order to maintain an adequate level of circulating glucose.

Much has been written lately concerning the use of the sulfur amino acids, notably methionine, in the treatment of liver damage due to widely different causes. The mode of action of methionine, as well as of other sulfur containing amino acids in providing protection against damage of the liver is not clear, although various hypotheses have been offered. These hypotheses vary all the way from the idea that the amino acids provide a source of readily available sulfur for direct combination with the noxious agent, to an indirect effect achieved through the lipotropic activity of the amino acid. In one laboratory it has been claimed that the protective effect of a diet high in protein against damage to the liver by chloroform can be attributed largely, if not wholly, to the methionine contained in the protein making up the diet.[18] Several reports on the use of methionine in the treatment of infectious hepatitis have recently appeared.[19, 20] The results of these experiments may be summarized by saying that in no instance were the results conclusive. A final statement on the worth of methionine in the treatment of acute hepatitis must wait, therefore, the appearance of further reports on the use of this type of therapy.

Patients presenting symptoms of severe infectious hepatitis may pose special problems with respect to the maintenance of nutrition. The patient may show a complete disinclination to eat for a period of several days. Anorexia, combined with an extraordinary tendency to lose weight

in the disease, may make the maintenance of a positive nitrogen balance difficult. Although the plasma protein concentration may show only slight alteration, there is good reason to assume that in the absence of an adequate protein intake a significant depletion in the stores of tissue protein may develop. In some cases a fall in serum albumin may be masked by an accompanying rise in serum globulin, so that the total serum protein concentration may appear unchanged. Moreover, a decrease in plasma protein is often accompanied by hemo-concentration, so that hypoproteinemia may not be perceptible unless determinations of the plasma volume are made at the same time. In order to provide adequate protein nutrition in the exceptional patient with infectious hepatitis who is unwilling to eat, the parenteral administration of a mixture of amino acids, such as that in a reinforced casein hydrolysate, may offer a practical solution to this difficulty. Several brands of casein hydrolysate are available at present for this purpose by means of which the entire protein requirement of a patient can be met for many days if the clinical state of the patient makes such parenteral administration imperative. Amino acid therapy to be of maximum effectiveness, must be supplemented with sufficient carbohydrate and fat to meet the caloric needs of the patient. Carbohydrate and amino acids may be given intravenously as a mixture. Unfortunately, the use of fat parenterally has not yet been achieved practically, so that only the oral route is available at present for its administration. Parenteral supplements of vitamins are available if desired. Except in the occasional case, however, when anorexia may provide a special need for vitamin supplements, a diet high in protein and carbohydrate with moderate fat meets readily the daily requirements of minerals and vitamins.

Bed rest, or at least limited activity, appears to be of paramount importance in the treatment of patients with infectious hepatitis. Retarded convalescence, or even recrudescence of the disease may occur following undue physical strain or exercise. Marked physical exertion, exposure to inclement weather, and convalescence from other diseases have long been associated with an increased susceptibility to infectious jaundice.[21] In this connection it may be recalled that in experimental transmission of infectious hepatitis to volunteers by means of filtrates of plasma from patients with the disease, physical strain incident to marching and manoeuvering was required in some cases to precipitate an attack.

The per cent of patients with infectious hepatitis who may be expected to develop signs of chronic liver disease is not known with certainty at the present time. In most groups the reported incidence has been low. However, objective criteria for residual damage were not met in many cases, or patients followed for long enough periods of time to have warranted the judgment that they had fully recovered. Establishment of adequate criteria to answer the question of whether or not residual damage to the liver has occurred following an attack of infectious jaundice is one of the many important problems which will tax the ingenuity of the post-war worker in the field of liver disease. Certainly a small number of patients may be expected to develop signs of chronic liver disease following an unusually severe or prolonged attack of acute infectious hepatitis. The syndrome seen in these cases is one characterized by mild jaundice and fixation of various hepatic functions at aberrant levels. The patient may recover in time or the disease may progress slowly and insidiously into a syndrome not unlike that of hypertrophic biliary cirrhosis, with or without ascites. In the treatment of these exceptional cases, those measures which have been found useful in the management of cirrhosis of the liver should be instituted.

Chronic Disease of the Liver

A syndrome consisting of a hard, stony liver with ascites, was known to Erasistratus, of Alexandria, nearly three hundred years before Christ. The disease was described later by Morgagni, Baillie and others in communications which have subsequently become medical classics. The term "cirrhosis" was applied to the syndrome by Laennec because the nodules projecting on the outer surface of the liver were "fawn or yellowish russet" in color. Many forms and varieties of cirrhosis have been described, but from the standpoint of supplying a basis for therapy there is little to be gained in a recital of the essential pathological characteristics of the lesions of cirrhosis. All forms, however, may be said to have in common three attributes, namely: (1) proliferation of connective tissue, (2) degeneration and death of hepatic cells, and (3) areas of regeneration of hepatic parenchyma.[22] There is eventually, in all long-standing affections, proliferation of connective tissue in the portal spaces with growth and extension of fibrous connective tissue into the whole hepatic lobule. The final stages of cirrhosis are accompanied by fusion of the peri-lobular connective tissue around the hepatic lobules with

subsequent deformation of the whole architectural pattern of the liver.

The pathogenesis of classical cirrhosis is obscure, and must remain so until more information is at hand concerning the development of the disease in its early stages and, perhaps, until it is possible to produce in animals a disease that is indistinguishable clinically and pathologically from cirrhosis in human subjects. It is an over-simplification of the facts to suppose that this has been done, although recent attempts with experimental dietary deficiencies have yielded results that permit us to hope that it may eventually be accomplished. Most students of the pathogenesis of classical cirrhosis agree that it is essentially a chronic diffuse inflammatory process which is initiated by an obscure type of injury, followed by proliferation of connective tissue in and about former sites of degeneration and necrosis.

For many years it has been the custom to regard fatty cirrhosis as a form of Laennec's cirrhosis. Indeed, Connor[23] has expressed the opinion that Laennec's cirrhosis is the ultimate outcome of a process of fatty infiltration. He has, moreover, described the various stages in which the syndrome described by Laennec is reached as (1) an acute fatty liver, attributable to alcohol in the main, changing slowly to a stage (2) of early but definite fibrosis, and finally (3) progressing to a classic nodular cirrhosis with reduction in size of the organ.[24] Recent experimental observations concerning the production of fatty infiltration of the liver with diets deficient in methionine and choline, and with rapid amelioration of the condition when the deficient agent is again supplied, make it appear that certain types of fatty cirrhosis belong in a separate category.

Therapy in Cirrhosis of the Liver

Chronic liver disease, with insufficiency, has posed and continues to present, one of the most complex problems of therapy which the physician encounters. Innumerable therapeutic measures have been devised within the past century in an attempt to cope with the problem of hepatic insufficiency, and with little success. Old remedies included potassium iodide, calomel, and a variety of saline purges such as vichy water and magnesium sulfate. Bile salts and other measures calculated to stimulate secretion of bile were employed with indifferent success. For a time it appeared that much might be accomplished through the use of diuretics such as acid forming salts and organic mercurials. Both

surgery and medicine provided new techniques for the treatment of cirrhosis. On the assumption that toxic agents were carried to the liver by the blood, various operations were devised by which attempts were made to shunt the blood carried by the portal vein into the general circulation. The operation of Talma, in which collateral circulation was achieved by suturing the peritoneal surface of the liver to the parietal peritoneum, had, and continues to have its advocates among members of the medical profession. Diverse as were these procedures, they had one thing in common, in that they were devised to relieve the chief complication of cirrhosis of the liver, ascites. The disease was regarded as fatal from the outset, and no hope was expressed that anything could be achieved other than securing greater comfort for the patient, and perhaps postponing exitus for a short time. From the time of the ancient physicians, medical writers have given cirrhosis of the liver a universally fatal prognosis, and nothing that has been achieved subsequently in the modern management of these patients has done much to alter this fatalistic concept.

Alcohol has always held a prominent place in the list of etiological factors proposed for cirrhosis of the liver, and as such has been particularly eschewed by the physician in planning a therapeutic regimen for his patients. The role of alcohol in the production of cirrhosis of the liver is still anything but clear. It would seem, however, that if alcohol is an important etiological factor in the production of the disease, that it is not due to its inherent toxicity for the liver, but rather to the factor of an associated disturbance in nutrition which is often an integral part of the syndrome of chronic alcoholism.

Attention was first directed to the role of faulty nutrition in the production of human cirrhosis of the liver by the studies of Rao, who in 1933 showed that a high incidence of this disease occurred among members of the population of Southern India, where alcoholism is all but unknown.[25, 26] In these areas nutritional deficiencies in protein, fat and vitamins, especially in vitamins A, C, and D, have occurred among members of the population for many years. In 1934, surveys made in Syria, where the incidence of cirrhosis is as high as it is in any part of the world, and where chronic alcoholism does not exist, showed that the diets of most members of the congested population were extremely low in protein. In Italy, in those regions where pellagra is endemic, the incidence of cirrhosis has always been high, as it has been in the southern

part of the United States, where pellagra has been a national problem since 1905. These facts, together with a growing awareness in this country of the relation betwen chronic alcoholism and vitamin deficiencies, have served to focus our attention on a possible nutritional basis for hepatic cirrhosis. This realization, together with a rapidly growing background in the production of experimental chronic liver disease in animals on diets low in protective substances has completely reoriented our therapeutic approach to the management of this distressing disease within the past several years.

Until the turn of the century, the diets prescribed by most physicians for patients with cirrhosis of the liver were generally low in all constituents. Carbohydrates were avoided because it was felt that excessive intestinal fermentation might arise, and prejudice the patient's clinical condition. Moreover, diets high in carbohydrate gave rise to diarrhea in many patients with chronic liver disease, thus providing another troublesome complication. Protein was avoided because it was believed that a damaged liver should not be further embarrassed by giving it protein to metabolize. Fat, too, was avoided on the basis that it would "stir up the bile" and add an additional load to the liver thereby. It is interesting in this connection to point out a rather glaring inconsistency, in that magnesium sulfate was prescribed at the same time in order to promote biliary secretion and drainage of the liver. Rationale for these various dietary restrictions were based on the knowledge of the central role of the liver in the breakdown of the constituents of food, and the belief that the liver should be "splinted" as it were, for the duration of the disease.

Around 1920 experiments were performed which showed that diets high in carbohydrate afforded a measurable degree of protection against intoxication with certain hepatoxic agents, such as chloroform, phosphorus, etc.[27] These observations ushered in the first really important change in the treatment of chronic liver disease from that which had been in vogue for many decades. The results achieved by Mann, who claimed that liver regeneration was depressed in dogs by diets high in protein, appeared for a time to call for diets low in protein, but sufficient carbohydrate was permitted to provide for a normal or even high total caloric intake.

Rationale for the administration of diets high in protein has been supplied from several fields of investigation. The importance of protein

in protecting the liver from damage was shown by Goldschmidt and his co-workers[28] in 1939 as a result of their dietary studies on rats, when it was concluded that a diet high in protein given before the production of prolonged chloroform anesthesia, reduced the incidence of hepatic cellular necrosis. Whipple and his associates[18] confirmed this work, and concluded, moreover, that the effects of a diet high in protein, in protecting the liver from chloroform damage, could be duplicated by the addition of methionine, and to a lesser extent of cystine, to a diet low in protein. Sebrell and associates[29] also demonstrated that in rats with cirrhosis of the liver produced by a diet low in choline and protein, improvement in the gross appearance of the liver, with hyperplastic regeneration of liver cells, occurred following treatment with choline and casein.

The rationale for a diet low in fat in the treatment of chronic liver disease stems from many sources, some valid, and some highly questionable. Obviously in the presence of obstructive lesions of the liver, the inclusion of a diet high in fat would be unwise, since under these conditions fats are not effectively digested. Also, it is known that certain lipotropic agents, such as choline and methionine, are effective in affording protection against certain types of experimental damage to the liver only if the diet is reasonably low in fat. There is some doubt, however, that the rational treatment of chronic diseases of the liver necessarily calls for a diet which is extremely low in fat. In the first place, it is impracticable to give a diet high in protein which at the same time contains little fat. Moreover, fats are rich sources of vitamins A, D, and E, and certain essential unsaturated fatty acids. Again, while it is stated that diets high in fat are displeasing to the average patient with liver disease, diets which are extremely low in fat are equally unpalatable and unappetizing. Finally, there is little evidence that diets with a moderate content of fat are prejudicial to patients with chronic liver disease.

Patek and his co-workers[30] were among the first to conclude that patients with alcoholic cirrhosis are benefited by supplements of the vitamins. It may be questioned, however, whether we should fasten the label of deficiency disease on the syndrome of cirrhosis of the liver. Certainly it cannot be regarded as an example of the classic types of deficiency diseases, such as beri-beri, scurvy, or pellagra. There is some reason, however, to regard cirrhosis of the liver as an *intrinsic* deficiency disease, in which faulty metabolism of certain essential components of

the diet may give rise to a syndrome which resembles deficiency diseases in some of its outward aspects, but which unlike the ordinary deficiency diseases does not respond in any striking or specific manner to one or a combination of vitamins.

The assumption that faulty metabolism of vitamins of the B-complex occurs in severe hepatic insufficiency is based thus far largely on speculation and analogy, since no convincing laboratory demonstration of this phenomenon has yet been made. Evidence that faulty metabolism of vitamin A occurs in patients with chronic disease of the liver is more convincing. Ninety-five per cent of the stores of vitamin A are in the liver, and analyses on cirrhotic livers for vitamin A levels reveal in many instances a concentration of less than 10 per cent of the normal amount. Patek and others[31] have shown that defects in dark adaptation may occur in patients with chronic liver disease of long standing. Night blindness and disturbances in dark adaptation in patients with hepatic insufficiency, however, are not greatly improved by the administration of vitamin A alone. Doses of vitamin A which are completely effective in the treatment of nyctalopia in patients with normal liver function are almost completely ineffective in relieving night blindness of patients with cirrhosis of the liver.[32] Beta-carotene, which is effective in uncomplicated nyctalopia, is also ineffective in the treatment of night blindness in patients with chronic disease of the liver. Since the liver is regarded as the only important site for the conversion of carotene to vitamin A, a part of the deficiency may arise as a result of the failure of the diseased liver to effect this conversion. Evidence of vitamin K deficiency in chronic liver disease is also excellent. This deficiency arises perhaps in part as a result of lowered absorption of vitamin K due to altered metabolism of the bile pigments, but chiefly it would seem, because of the faulty utilization of the vitamin by the liver. Only when considerable liver function remains in chronic disease of the liver is vitamin K effective in enhancing the prothrombin value. Patients with long-standing cirrhosis of the liver may develop a syndrome characterized by osteoporosis and osteomalacia. Here, too, although the clinical symptomatology is strongly reminiscent of chronic vitamin D deficiency, the syndrome is neither prevented nor cured by the administration of vitamin D.[32]

Evidence, therefore, is good that faulty metabolism of the fat soluble vitamins may occur as a result of chronic damage to the liver. One is

tempted to speculate on the possibility that interference with the metabolism of the water-soluble group of vitamins also occurs in severe hepatic insufficiency, although more evidence is needed to provide proof that this phenomenon occurs. Although the assumption continues to be made on clinical grounds, no evidence as clear cut as that for the aberrant metabolism of the fat soluble vitamins exists for faulty metabolism of the vitamins of the B group in cirrhosis of the liver. That deficiency in the case of vitamins A, D and K is essentially intrinsic, in contradistinction to the classical type of deficiency arising from lowered intake of these substances, is revealed in the failure to achieve satisfactory reversal of the syndrome by providing an ample supply of vitamins A, D or K, either by oral or parenteral route.

In connection with the idea that in chronic liver disease there is faulty metabolism or activation of the vitamins, it is tempting to regard other metabolic aberrations in chronic liver disease as being due to the failure of the liver to achieve synthesis of specific catalytic proteins, such as the enzymes, in sufficient quantities to meet the demands of normal metabolism. Fibrinogen, prothrombin and albumin are examples of three proteins which have their site of synthesis in the liver, and the synthesis of which is materially depressed in chronic hepatic insufficiency. There are probably many more examples of essential proteins of which the rate of synthesis is lowered in chronic liver disease, but we lack adequate techniques for their demonstration.

Most specific catalytic substances, organic as well as mineral, appear to require special protein vehicles for proper intermediation of their functions. It is possible, therefore, that the type of deficiency which we have labelled intrinsic, for want of a better term, may arise not as a result of lowered intake of the prosthetic catalyst, but through a depression in the rate of synthesis of the specific protein carrier needed to render the catalyst effective metabolically. The thiamino-proteins, and the proteins required as vehicles for the flavin and pyridine compounds might serve as examples, a deficiency in the synthesis of which would result conceivably in the production of symptoms not unlike those observed in thiamin, riboflavin and nicotinic acid deficiencies, respectively.

Optimism with respect to therapy of advanced cirrhosis of the liver is nearly always met with the statement that since much of the defect in cirrhosis appears to be a mechanical one brought about by fibrosis

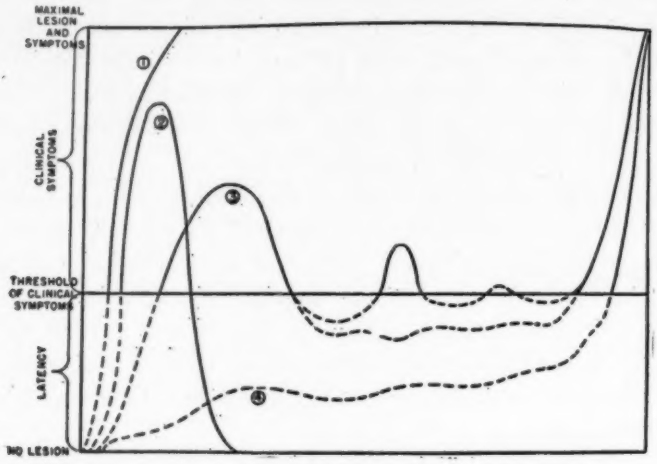
and atrophy of the liver, attempts to reverse the pathologic process are hopeless from the outset. Various explanations have been offered, for example, for the ascites which occurs in the chronic stages of disease of the liver, particularly of the Laennec type. The most common explanation for this phenomenon has been that of portal hypertension and consequent resistance to the flow of blood from the portal system through the liver. It is true that a portal hypertension may exist in many of these cases. It has been observed, however, that there are many instances when portal hypertension is marked in the absence of ascites. In other cases ascites has been recorded in the presence of a normal or only slightly elevated pressure in the portal system. Patek and Post[33] concluded that the ascites is related more directly to a deficit in plasma albumin, with consequent diminution in the colloid osmotic pressure of the blood. They have, moreover, concluded that when the concentration of albumin reaches 3.2 grams per 100 cc. of plasma, ascites disappears rapidly, although no demonstrable change has occurred in the meantime in the portal pressure. Ralli, Hoagland and collaborators[34] have shown, however, that in cases which have been treated with a regimen of combined therapy, consisting of a diet high in protein and carbohydrate and the administration intravenously of large quantities of crude liver extract, ascites may disappear and the patient show marked clinical improvement for months before any demonstrable change has occurred in the level of plasma albumin. These observations suggest that the level of albumin in the plasma is not the sole determining factor in the production of ascites. In 1940 Robinson and Farr[35] reported the presence of an antidiuretic factor in the urine of patients with nephrosis and premenstrual edema. On the premise that a similar substance might be present in the urine of patients with cirrhosis and ascites, the antidiuretic effect of aliquots of dialyzed urine from the patients was studied by Ralli *et al.* Normal urine has only slight antidiuretic activity. The urine of patients with cirrhosis of the liver and ascites was found to possess a marked antidiuretic effect when injected into hydrated rats. However, there was little or no increase of antidiuretic substance over the normal in the urine of patients with cirrhosis without ascites. Moreover, the magnitude of the effect seemed to parallel the degree of ascites.

The antidiuretic substance excreted in the urine by patients with cirrhosis of the liver and ascites has its origin presumably from the posterior pituitary, although that this is actually the case cannot be

stated at this time. That aberrant metabolism of other hormones may occur in cirrhosis of the liver is becoming increasingly certain. It is also evident that aberrant metabolism of some hormones in chronic liver disease may arise through the inability of the diseased liver to accomplish their inactivation or alteration. Certain changes associated with gynecomastia, and testicular atrophy in the male, in cirrhosis of the liver, are thought to arise as a result of the inability of the diseased liver to accomplish the inactivation of estrogen.[36, 57] Free circulating estrogen is known to be high in cirrhosis, and it may well be that certain further changes having to do with aberrant water and electrolyte metabolism in patients with chronic disease of the liver may be attributed in part to a disturbed balance between the concentration of male and female hormones arising as a result of the inability of the liver to accomplish their proper metabolism.

It would seem that many clinicians do not think that patients with active liver disease should necessarily be restricted in their physical activity. Most physicians would not dream of permitting unrestricted activity in patients suffering from impaired function of a comparable degree in other organs, such as the lungs or heart. Rest and freedom from undue physical activity is accepted as correct management in patients presenting signs of cardiac and renal insufficiency. Yet many practitioners fail to treat acute or chronic hepatitis, in which extensive damage to the liver is evident, with equal consideration. That rest or restriction of activity at once reduces the functional demands on the liver is evident from a consideration of elementary principles of physiology. Moreover, it permits careful control of the diet and medication to a degree not possible in the ambulant patient.

Aside from general measures directed toward relief of hypoproteinemia and anemia by transfusion of blood and plasma, certain specific measures directed toward relief of possible intrinsic deficiencies have been advocated from time to time. For example, marked symptomatic improvement often occurs in patients with chronic liver disease when an unrefined, water soluble extract of liver is administered parenterally. For some time we have been engaged coöperatively with Elaine P. Ralli of the Third Medical Division, Bellevue Hospital, in trying to evaluate objectively the effect of liver extract, given intravenously, as a form of replacement therapy in hepatic insufficiency.[27, 34] For this purpose a crude water soluble extract of Cohn's liver fraction G has been prepared



Variations in the course of hepatitis. *1*, Acute hepatitis progressing rapidly to death; *2*, acute hepatitis with recovery; *3*, acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis; *4*, hepatitis latent from the start until advanced liver insufficiency supervenes. (Bloomfield, courtesy of Am. J. Med. Sci.)

at the Rockefeller Hospital which can be given with comparative safety in large quantities by the intravenous route, provided careful tests for tolerance and sensitivity are carried out beforehand. By use of the intravenous route large amounts of liver extract can be given without the marked discomfort attendant on the continued use of potent crude extracts of liver designed for intramuscular use. While preliminary results have been encouraging, it is much too early to claim any extraordinary merit for this form of therapy. In any case, it can be used successfully only in conjunction with a full regimen of therapy which includes diet, rest, and numerous supportive measures indispensable to proper management of patients with chronic liver disease.

In the foregoing review, an effort has been made to show the influence which recent information in the field of metabolism and nutrition has had on the development of our present concept of rational treatment for hepatic insufficiency. Although we are yet far from the ultimate goal of satisfactory therapy for the hepatic diseases, some definite progress has been made, and the hope is very bright that as more

information is secured concerning the metabolic processes at work in the normal and diseased liver, increasing success in the therapy and management of these distressing disorders will be achieved.

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